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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/796,164	STAMLER ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,14-22,27-29,40,41,43,44,46,63,65 and 69-81* is/are pending in the application.

4a) Of the above claim(s) *70,71 and 73-80* is/are withdrawn from consideration.

5)☒ Claim(s) *43,44,46,63 and 65* is/are allowed.

6)☒ Claim(s) *11,12,14-22,27-29,40,69,72 & 81* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet.*

Continuation of Attachment(s) 6). Other: Feb. 13, 2001 Interview Summary Record.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status Of The Claims

Claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65 and 69-81 are currently pending.

Claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 are under consideration.

Claims 70, 71, 73-80 are withdrawn from consideration as being directed to a nonelected invention.

A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection(s) and/or Rejection (s)

The rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Stamler WO93 as applied to claims 16, 20-22, 27-28 and 40 above, and further in view of Moore et al., J.Biol. Chem. Vol. 251, No. 9, (5/76) pages 2788-2794 or Sharma et al., J. Biol. Chem. Vol. 253, No. 18 (9/78) pages 6467-72 is hereby withdrawn in view of applicant's arguments.

The rejection of claims 11-12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 of this application conflict with claims which are present in Application No.08/667,003 (US Pat. No. 6,197,745) and 08/796,164. 37 CFR 1.78(b) is hereby withdrawn in light of the filed terminal disclaimers.

Allowable Subject Matter

2. Claim 41 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

3. The following is a statement of reasons for the indication of allowable subject matter: The method of delivering NO by administering nitrosylhemoglobin was neither disclosed nor suggested in the prior art of record. Additionally, it was unexpected that nitrosylhemoglobin could act physiologically as an NO donor due to the low dissociation constants of heme bound NO groups as pointed out by applicant.

Claims 43, 44, 46, 63 and 65 are allowed.

Outstanding Objection(s) and/or Rejection (s)

4. Claims 16, 20-22, 27-28 and 40 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

The Stamler refence teaches methods for "increasing blood oxygen transport by hemoglobin and myoglobin" which include the use of NO donating proteins including hemoglobin. E.g. see abstract.

Additionally, Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, vasodilators and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

Similarly to low molecular weight thiols, the Stamler reference further teaches that proteins (including hemoglobin), which are nitrosylated on oxygen, carbon or nitrogen sites possess the same therapeutic utility as nitrosylated/nitrated low molecular

weight thiol compounds. (E.g. see page 6, lines 13-15; page 7, lines 17-21; and claims).

The reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Further it is known in the art that hemoglobin is involved in regulating oxygen metabolism by its ability to bind reversibly to blood oxygen and thus facilitate the capability of blood to transport oxygen to bodily tissues (e.g. see bottom of page 19-top of page 20).

Accordingly, it would have been obvious to combine a low molecular weight thiol or nitrosothiol with either hemoglobin or nitrosated hemoglobin to deliver oxygen or NO (e.g. claim 16) since the Stamler reference teaches the use of the same compounds separately to effectuate the same function and in conjunction with hemoglobin to increase blood oxygen transport (e.g. see abstract).

Additionally, the use of Nitrosated/Nitrated proteins, including nitrosated/nitrated hemoglobin to deliver NO to tissues (e.g. claim 40) in order to effectuate the treatment of abnormalities or diseases which are mediated by nitric oxide and oxygen metabolism (e.g. lung disease, sickle cell anemia, heart disease, high blood pressure etc.) would

have been obvious since the reference discloses the use of nitrosated proteins, including nitrosated hemoglobin, to treat such disease states.

Discussion

Applicant's arguments directed to the above obviousness rejections over the WO 93 reference were considered but deemed nonpersuasive for the following reasons.

Applicant first argues that the WO 93 reference fails to teach a method of making S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed January 6, 1999 attacking Example 19 of WO 93; nor does the WO 93 reference appreciate methods as disclosed in the present specification. Applicant further argues that the WO93/09806 fails to demonstrate "any S-nitrosylation of hemoglobin"or "any modified form of hemoglobin with increased oxygen binding capacity".

Initially it is noted that this argument is not persuasive since it's not commensurate to the presently claimed invetion which is not so limited. The claims broadly address the use of "nitrosyl/nitrosated/nitrated hemoglobins" or "one or more nitrosyl-heme containing donors of NO" which encompass Hb nitroslation/nitration at other sites other than thiols or metals. See e.g. specification pages 26-27 for definitions.

Additionally, this argument is not persuasive since the reference teaches the use of nitrosylated hemoglobins which includes NO groups attached to "additional sites such as oxygen, carbon and nitrogen" (e.g. see Abstract; page 6) and is not so limited to nitrosylhemoglobin or S-nitrosylhemoglobin.

Regarding S-nitrosylation of proteins including hemoglobin , Stamler WO93 discloses different methods for thiol nitrosylation of proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93 further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Regarding the use of "excess" nitrosating agent, and the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin it is noted that

the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 (addressed in the Stamler Declaration) as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested

by the WO 93 reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH 7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26). Optimization of reaction conditions, including pH, is within the skill of the art.

Accordingly, the WO 93 reference clearly teaches synthesizing thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, with further optimization of pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Applicant alludes to a telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler on February 13, 2001 referring to the Stamler 132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

According to the "Interview Summary Record" mailed to applicant on 10/22/03 under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" the Examiner states that "Applicant presented arguments to traverse the rejections of record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding

the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed to applicant on 10/22/03 is attached hereto.

Regarding Claim 16 applicant further argues that the WO 93 reference fails to teach the use of "nitrosylhemoglobin" (e.g. NO adduct on the heme Fe preventing the binding of oxygen) as an "NO donor" and thus can not meet the claim 16 limitation of "potentiating delivery of NO". In this regard, applicant argues that they discovered (e.g. specification Example 15) the inherent conversion (upon administration of nitrosylhemoglobin) in the lung under physiological conditions of "nitrosylhemoglobin" to SNO-hemoglobin which then acts as an NO donor and potentiates delivery of NO to mammalian tissues.

This argument was considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that claim 16 is directed to a method of "potentiating delivery of NO" to mammalian tissues by administering to a mammal:

a. Low molecular weight thiol + hemoglobin or

b. Low molecular weight thiol + "nitrosated hemoglobin".

Accordingly applicant's argument regarding "nitrosylhemoglobin" which is a species of the generic "nitrosated hemoglobin" (e.g. see specification pages 26-27 for definitions) is not commensurate in scope to the presently claimed invention.

Secondly, applicant's argument fails to address the WO 93 reference teaching of the making of NO donating proteins by nitrosylation of proteins, including hemoglobin,

at positions other than the heme Fe (e.g. thiol, oxygen, carbon, or nitrogen). In this regard, the reference clearly teaches nitrosylated protein derivatives (including hemoglobin) which act as NO donating compounds (e.g. potentiate NO tissue delivery) upon administration to mammals.

Applicant argues that the WO 93 reference fails to teach the combination of a low molecular weight thiol with hemoglobin or nitrosated hemoglobin in a method to "potentiate delivery of NO" (e.g. act as NO donors) arguing that WO 93 solely teaches the use of "low molecular weight thiols" to thiolate proteins.

This is not persuasive since the WO 93 reference clearly teaches nitrosylation of proteins *AND "low molecular weight thiols" which include amino acids containing thiol groups* (e.g. cysteine, homocysteine and N-acetylcysteine) for therapeutic use resulting from their ability to "deliver nitric oxid". See Abstract; pages 1-2; see also claims including (but not limited to) claims 36-41.

Regarding claim 16 (directed to the use of a low molecular weight thiol with hemoglobin or "nitrosated hemoglobin") Applicant argues that the reference fails to teach the combination of hemoglobin with a low molecular weight (nitroso) thiol or nitrosated hemoglobin.

Applicant's argument is not persuasive since the reference clearly teaches the incorporation of NO donating compounds including low molecular weight (nitroso) thiols and nitrosated hemoglobins in conjunction with the use of hemoglobin to increase oxygen transport. See e.g. the WO 93 abstract.

Additionally, the above rejection is an obvious rejection. The combination of a nitrosylated protein with a nitrosylated amino acid containing a thiol group (e.g. low mw thiol) is readily obvious from the disclosed and claimed use of these agents separately in the same methods. Applicant is again referred to the WO 93 disclosure (e.g. abstract; pages 1-2 etc. and claims).

Applicant further argues that the reference fails to teach thiols as regulating oxygen metabolism and hemoglobin as being NO donating and thus no additive effects of combining these different compositional components.

This argument is not persuasive since compositional components are not always added together for purposes of additive properties. In the present instance the reference provides motivation to combine hemoglobins' blood oxygen transport properties with the complementary benefits imparted by an NO-donating protein and/or NO-donating thiol containing amino acid (e.g. low molecular weight thiol).

With regard to claims 20-22, 27 and 28 applicant argues that the present claims encompass the use of "nitrosated hemoglobins" which include SNO hemoglobin and nitrosylhemoglobin and that the WO reference fails to enable the formation of SNO hemoglobin or specifically address the use of nitrosylhemoglobin in the presently claimed methods. Further, with regard to claim 40, applicant argues that the WO 93 reference fails to teach the use of "nitrosyl-hemoglobin" as being useful in the claimed method.

Applicant's arguments were considered but are not deemed persuasive for the following reasons.

Initially, Applicant's argument is not persuasive since applicant's arguments are not commensurate to the scope of the presently claimed inveniton (e.g. claims 20-22,27, 28 and 40) which are not limited to nitrosylhemoglobin or SNO hemoglobin.

Applicant's argument regard the nonenablement of SNO hemoglobin has already been addressed above.

Additionally, applicant's argument fails to appreciate the reference teaching as a whole in which the reference teaching of the therapeutic use of nitrosylated/nitrosated hemoglobin genus (e.g. in general) would include polynitrosatedhemoglobins; e.g. the reference teaching of thiolating proteins (e.g. hemoglobin) /amino acids at positions other than at thiols (or metal), including oxygen, carbon and nitrogen for achieving regulation of protein/amino acid function; such derivatives being within the scope of the presently claimed broad "nitrosated hemoglobin" generic.

Accordingly, the above obviousness rejections are hereby maintained.

5. Claims 11-12 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler WO 93/09806 (5/93).

The presently claimed invention is directed to producing a composition comprising either SNO-Hb[FeII]O2 (produced in the presence of oxygen) or SNO-Hb[FeII] (produced in the absence of oxygen) by reacting "excess nitrosating agent" with purified hemoglobin (e.g. claims 10-11 and 13-14). Claims 12 and 15 specifically select a low molecular weight S-nitrosothiol as the nitrosating agent.

Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

However, the above two reference methods for thiol nitrosylation fail to disclose the use of "excess" nitrosating agent, and preferably the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin.

But the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under

physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).
Optimization of reaction conditions, including pH, is within the skill of the art.

Additionally, it is a matter of obvious design choice to select anaerobic conditions for making a deoxygenated hemoglobin derivative and aerobic conditions when desiring to make an oxygenated hemoglobin derivative.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to synthesize thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, and to further optimize pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the reference example for making S-nitrosylated hemoglobin (e.g. Example 19) teaches using pH of 6.9 and the reference fails to exemplify the making of S-nitrosylated hemoglobin at pH of 7.4 or higher.

This argument is not persuasive since the rejection above is raised under obviousness and not anticipation.

Applicant argues that stability of SNO-tPA at pH 7.4 does not reveal anything about the reaction conditions under which it can be made ; and applicant further argues that the reaction conditions for making SNO-tPA are not analogous to those conditions for making S-nitrosylated hemoglobin in Example 19.

This argument was considered but deemed nonpersuasive for the following reasons.

Applicant's argument fails to consider the Stamler reference teaching as a whole which address both the syntheses of S-nitrosylated proteins other than hemoglobin (e.g. tPA, BSA etc) and storage of the resulting thiol proteins at pH 7.4 as well as the stability of the SNO bonds of these proteins under physiologic conditions at pH 7.4. Accordingly, the reference provides ample motivation for one of ordinary skill in the art to optimize pH to pH 7.4 in light of the reference teaching.

Accordingly, the above obviousness rejection is maintained.

6. Claims 17-19, 29, 69, 72 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feola et al. , U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Stamler WO 93/09806 (5/93).

Feola et al. disclose the state of the prior art regarding "blood substitutes" as being an emergency resuscitative fluid that:

a. Restores blood volume;

b. Transports oxygen;

c. Reduces vasoconstiction. See Feola col. 1.

Feola et al. disclose the use of "blood substitutes" which comprises hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7).

The Feola reference "blood substitute" composition and intended use thereof (e.g. treat sickle cell anemia) differs from the presently claimed invention which utilizes nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol instead of hemoglobin or hemoglobin combined with glutathione.

However, Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, **vasodilators** and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

The Stamler reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Thus, the Stamler et al. reference provides the skilled artisan with motivation to utilize nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol to make a blood substitute for treating sickle cell anemia in order to increase blood volume, oxygen delivery and reduce vasoconstriction as effected by nitrosated hemoglobins alone or in conjunction with a nitrosothiol.

Accordingly, it would have been obvious to the skilled artisan at the time of applicant's invention to make a blood substitute comprising nitrosated hemoglobin alone or in conjunction with a low molecular weight nitrosothiol for their expected benefits as suggested by the Stamler reference and in analogous manner as the Feola reference composition..

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the the Feola et al. or the Stamler WO93 references fail to teach S-nitrosothiol in a blood substitute. Additionally, it is alleged that the hemoglobin composition of Feola fails to teach nitrosated/nitrated hemoglobin.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined teaching of the Feola and Stamler WO93 references arrive at the presently claimed invention for the reasons provided above.

Arguments presented against the Stamler reference already addressed by the Examiner in previous obviousness rejections over this reference (e.g. arguments not commensurate; teaching of nitrosylated thiol amino acids as NO donors; etc.) are specifically incorporated by reference in their entirety and not included here.

Applicant argues that "an effect of hemoglobin-based blood substitutes has been vasoconstriction" (citing Feola, last sentence of column 4).

This argument is not persuasive since the Feola reference addresses the prior art vasoconstriction problem by using a derivatized hemoglobin; and the above obviousness rejection addresses why one would be motivated to substituted the Feola derivatized hemoglobin with the Stamler WO93 derivatized (e.g. nitrosylated) hemoglobin to arrive at the presently claimed invention.

Accordingly, the above obviousness rejection is hereby maintained.

7. Claims 69 and 72 are rejected under 35 U.S.C. 102(e,f) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. U.S. Patent No. 6,291,424 (9/18/01: filed March 1995 or earlier).

The Stamler patent discloses and claims compositions comprising a narrow genus of S nitrosated/nitrosylated heme proteins which include hemoglobin within the scope of the presently claimed invention. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above 102/103 rejections were considered but deemed nonpersuasive for the following reasons.

Applicant argues that "The teachings of Stamler et al. (US Patent No. 6,291,424) are those of WO 93/09806" and the WO 93 reference fails to teach a method of making

S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed January 6, 1999 attacking Example 19 of WO 93.

Initially, it is noted that the claimed subject matter of US Pat. No. 6,291,424 is presumed valid e.g. enabled.

With respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,291,424 disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Regarding the use of "excess" nitrosating agent, and the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin it is noted that .

the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 (addressed in the Stamler Declaration) as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO

serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the WO 93 reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26). Optimization of reaction conditions, including pH, is within the skill of the art.

Accordingly, the WO 93 and the issued patent reference clearly teaches synthesizing thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, with further optimizization of pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Applicant alludes to a telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler on February 13, 2001 referring to the Stamler 132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

According to the "Interview Summary Record" mailed to applicant on 10/22/03 under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" the Examiner states that "Applicant presented arguments to traverse the rejections of record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed to applicant on 10/22/03 is attached hereto.

Accordingly, the above rejection is hereby maintained.

8. Claims 21, 22, 27, 28, 40, 69 and 72 are rejected under 35 U.S.C. 102(e,f) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,583,113 (6/03: filed 3/95 or earlier).

Stamler et al teaches (claims and discloses)compositions comprising nitrosylated heme proteins (including (S) nitrosated/nitrosylate hemoglobin) and the use thereof to deliver NO to tissues for the prevention/treatment of various diseases/disorders including cardiovascular diseases/disorders (e.g. ARDS, heart disease etc.) . See e.g. col .1-2 ; col. 4; col. 5; col. 9-12; examples; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above 102/103 rejection over the 6,583,113 patent were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified to remove claim 41 which is specifically directed to "nitrosylhemoglobin" thus rendering moot arguements directed thereto.

Applicant argues that "There is no evidence presented in US Patent No. 6,583,113 that any form of nitrosated or nitrated hemoglobin has any biological activity that can be applied to any disease or medical condition".

This argument was considered but deemed nonpersuasive for the following reasons.

The rejection above clearly points out that Stamler et al '113 patent reference teaches (claims and discloses)compositions comprising nitrosylated heme proteins (including (S) nitrosated/nitrosylate hemoglobin) and the use thereof to deliver NO to tissues for the prevention/treatment of various diseases/disorders including cardiovascular diseases/disorders (e.g. ARDS, heart disease etc.) . See e.g. col.1-2 ; col. 4; col. 5; col. 9-12; examples; patent claims.

Applicant further alleges that "One of ordinary skill in the art would conclude from Example 19 of 6,583,113 that the syntheses of SNO-hemoglobin failed".

This argument is not found persuasive since applicant has not provided sufficient facts or other evidence sufficient to challenge the presumed validity afforded US Pat. No. 6,583,113.

Further, with regard to claim 40, applicant argues that the '113 patent reference fails to teach the use of "nitrosyl-hemoglobin" as being useful in the claimed method.

Applicant's arguments were considered but are not deemed persuasive for the following reasons.

Applicant's argument is not persuasive since applicant's arguments are not commensurate to the scope of the presently claimed inveniton which are not limited to nitrosylhemoglobin, but encompass other species of nitrosylated heme containing NO donating compounds including thiolated hemoglobins. In this respect, Applicant's argument fails to appreciate the patent reference teaching as a whole in which the reference teaching of the therapeutic use of nitrosylated/nitrosated hemoglobin genus (e.g. in general) would include polynitrosatedhemoglobins; e.g. the reference teaching of thiolating proteins (e.g. hemoglobin) /amino acids at positions other than at thiols (or metal), including oxygen, carbon and nitrogen for achieving regulation of protein/amino acid function; such derivatives being within the scope of the presently claimed broad "nitrosated hemoglobin" generic.

Applicant argues that the teachings of Stamler et al. (US Patent No. 6,583,113:Example 19) is equivalent to WO 93/09806; and that the WO 93 reference fails to teach a method of making S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed January 6, 1999 attacking Example 19 of WO 93.

Initially it is noted that this argument is not persuasive since it's not commensurate to the presently claimed invention which is not so limited. The claims broadly address the use of "nitrosyl/nitrosated/nitrated hemoglobins" or "one or more

nitrosyl-heme containing donors of NO" which encompass Hb nitroslation/nitration at other sites other than thiols or metals. See e.g. specification pages 26-27 for definitions. Accordingly, the Stamler references (WO 93 and 6,583,113) teach the use of nitrosylated hemoglobins which includes NO groups attached to "additional sites such as oxygen, carbon and nitrogen" (e.g. see Abstract; page 6) and is not so limited to nitrosylhemoglobin or S-nitrosylhemoglobin.

Secondly, the claimed subject matter of US Pat. No. 6,583,113 is presumed valid e.g. enabled.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,583,113 disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Regarding the use of "excess" nitrosating agent, and the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin it is noted that .

the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of

acidic Na NO2 (addressed in the Stamler Declaration) as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Additionally, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the WO 93 reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26). Optimization of reaction conditions, including pH, is within the skill of the art.

Accordingly, the WO 93 and the issued patent reference clearly teaches synthesizing thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, with further optimizization of pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Applicant alludes to a telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler on February 13, 2001 referring to the Stamler

132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

According to the "Interview Summary Record" mailed to applicant on 10/22/03 under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" the Examiner states that "Applicant presented arguments to traverse the rejections of record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed to applicant on 10/22/03 is attached hereto.

Accordingly, the above rejection is hereby maintained.

9. Claims 16-22, 27- 29, 40, 69, 72 and 81 are rejected under 35 U.S.C. 102(e,f) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier).

Stamler et al. teach compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference

teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above 102/103 rejection were considered but deemed nonpersuasive for the following reasons.

Applicant alleges that 6,471,978 (col. 19, lines 6-19)describes methods of producing S-nitroso proteins which are not enabling to one of ordinary skill in the art since no information on the stability of any hemoglobin derivative is give, or on its suitability as a coating for a medical device.

This argument is not found persuasive since applicant has not provided sufficient facts or other evidence sufficient to challenge the presumed validity afforded US Pat. No. 6,471,978.

Regarding claim 16, applicant alleges that the '978 patent fails to teach the combination of a low molecular weight thiol with Hb or "nitrosated Hb" to potentiate NO delivery.

This argument was considered but deemed nonpersuasive for the following reasons.

As pointed out in the rejection above, the '978 patent teaches medical devices inserted in a patient which includes "a surface which exposes and delivers a form of nitric oxide to vascular surfaces with which it comes in contact" thus defining the term "nitric oxide adduct". See e.g. col. 1, lines 15-25. The reference discloses AND CLAIMS (E.g. claim 1) in vivo delivery of "at least one nitric oxide adduct" which is selected from a small group including "nitrosothiols" and "nitrosated amino acids" (e.g. "low molecular weight thiols" within the scope of the present claims) as well as "nitrosoproteins" including

within a small list "S-nitrosohemoglobin" (e.g. a "nitrosated Hb" within the scope of the presently claimed invention: e.g. see patent claim 40). Additionally, it is noted that the patent claims explicitly teach the NO donating ability of such NO adducts. E.g. see patent claims 13 and 49. Accordingly, the '978 patent clear anticipates or alternatively renders obvious therapeutic administration of low molecular weight thiols (e.g. nitrothiols or nitrosylated thiol containing amino acids) and "nitrosated Hb's" to potentiate NO delivery.

Accordingly, the above rejection is hereby maintained.

10. Claims 69 and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,291,424 (9/18/01: filed March 1995 or earlier).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims are directed to compositions comprising a narrow genus of S nitrosated/nitrosylated heme proteins which include hemoglobin within the scope of the presently claimed inveniton. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above obviousness-double patenting rejection over the '424 patent was considered but deemed nonpersuasive for the following reasons.

Applicant argues that the office erroneously failed to arrive at the correct inventorship result regarding a Rule 1.63 petition.

This argument is not persuasive since the issued patent, presumed valid, lists Dr. Stamler as an inventor.

Accordingly, the above double patenting rejection is hereby maintained.

11. Claims 69 and 72 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/835,038 (PG PUB US 2002/0052314A1 May 2, 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S- nitrosated/nitrosylated hemoglobin which comprise a small number of deoxy- and oxy- (which are obvious variants or each other) hemoglobin species (e.g. 4 species deoxy/oxy nitrosated/nitroyslated Hb) which would include S-nitrosylated hemoglobins). Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion

Applicant's argument directed to the above provisional obviousness double patenting rejection was considered but deemed nonpersuasive for the following reasons.

Applicant argues that Dr. Stamler is refusing to sign the Declaration indicating he is not an inventor of the 09/835,038.

Accordingly, the above obviousness double patenting rejection is retained since Dr. Stamler, at this time, is still indicated to be an inventor of the 09/835,038 application.

12. Claims 19-22, 27-28, 40, 69 and 72 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 (especially claims 7-9 and 17) of copending Application No. 10/216,865 (PG PUB US 2003/0007967A1 Jan 9, 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S-nitroso hemoglobins and uses thereof which comprise NO delivery, including treating/preventing cardiovascular/respiratory disorders (e.g. Heart disease, ARDS etc: see patent claim 9 interpreted in light of disclosure: e.g. at page 6) . Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The adminsitration of hemoglobins to patients for the treatment of cv/pulmonary disorders would inherently result in the scavenging of oxygen free radicals and/or the reduction of blood pressure (e.g. vasodilatory effect).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion

Applicant's argument directed to the above provisional obviousness double patenting rejection was considered but deemed nonpersuasive for the following reasons.

Applicant argues that Dr. Stamler is refusing to sign the Declaration indicating he is not an inventor of the 10/216,865.

Accordingly, the above obviousness double patenting rejection is retained since Dr. Stamler, at this time, is still indicated to be an inventor of the 10/216,865 application

13. Claims 21, 22, 27, 28, 40, 69 and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,583,113 (6/03).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims teach compositions comprising nitrosated/nitrosylated heme proteins (e.g.including S-nitrosylated hemoglobins : see cliams 1-3) and their use (E.g. delivery of NO to tissues via administration) in treaing/preveinting diseases including cardiovascular diseases such as ARDS (E.g. see claims 1 and 4:col. 11-12) and heart disease.

Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments directed to the above obviousness-double patenting rejection over the '424 patent was considered but deemed nonpersuasive for the following reasons.

Applicant argues that the office erroneously failed to arrive at the correct inventorship result regarding a Rule 1.63 petition.

This argument is not persuasive since the issued patent, presumed valid, lists Dr. Stamler as an inventor.

Applicant further argues that claims 21,22,27,28,40,41,69 and 72 are patentably distinct from and nonobvious from claims 1-4 of US Pat. No. 6,583,113 since none of claims 1-4 of '113 are composition claims (as compared to present claim 69 and 72) nor do claims 1-4 comprise a step of administering to a mammal/human a nitrosated/nitrated hemoglobin, or a nitrosyl-heme containing donor of NO.

This argument is not persuasive since patent claim 1 clearly teaches compositions comprising thiol nitrosylated (polynitrosylated) hemoglobins for therapeutic use thus rendering obvious the compositions themselves as well as their use.

Applicant's argument regarding the patented therapeutic method reading on "a process that occurs in nature" is not understood.

Accordingly, the above double patenting rejection is hereby maintained.

14. Claims 16, 20-22, 27-28, 40, 69 and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 of Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier) as interpreted in light of the specification regarding the scope of treatment of vasculature damage and inherency.

Stamler et al. teach (e.g. disclose and claim) compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon

administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g vascular disease: see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See all the patent claims, particularly 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as

immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

Discussion

Applicant's arguments were considered but deemed partially persuasive. Accordingly, the above rejection has been modified to remove claims 17-19, 29 and 81 directed to blood substitutes.

Applicant's arguments directed to present claims 69 and 72 (drawn to compositions comprising S-nitrosylated oxy(deoxy)hemoglobin) were considered but deemed nonpersuasive since the reference teaching of the use of compositions comprising S-nitrosylated hemoglobins would render obvious the compositions themselves.

Regarding claim 16, applicant alleges that the '978 patent fails to teach the combination of a low molecular weight thiol with Hb or "nitrosated Hb" to potentiate NO delivery.

This argument was considered but deemed nonpersuasive for the following reasons.

As pointed out in the rejection above, the '978 patent teaches medical devices inserted in a patient which includes "a surface which exposes and delivers a form of nitric oxide to vascular surfaces with which it comes in contact" thus defining the term "nitric oxide adduct". See e.g. col. 1, lines 15-25. The reference discloses AND CLAIMS (E.g. claim 1) in vivo delivery of "at least one nitric oxide adduct" which is selected from a small group including "nitrosothiols" and "nitrosated amino acids" (e.g. "low molecular

weight thiols" within the scope of the present claims) as well as "nitrosoproteins" including within a small list "S-nitrosohemoglobin" (e.g. a "nitrosated Hb" within the scope of the presently claimed invention: e.g. see patent claim 40). Additionally, it is noted that the patent claims explicitly teached the NO donating ability of such NO adducts. E.g. see patent claims 13 and 49. Accordingly, the '978 patent clear anticipates or alternatively renders obvious therapeutic administration of low molecular weight thiols (e.g. nitrothiols or nitrosylated thiol containing amino acids) and "nitrosated Hb's" to potentiate NO delivery.

Applicant queries why the Examiner refers to the patent specification when the patent claims, for purposes of double patenting are at issue; and questions the applicability of *In re Schaumann* decision in the present context (e.g. double patenting rejection). Accordingly, Applicant argues that the therapeutic method claims 20-22, 27 and 28 are not rendered obvious by the patented methods (e.g. treating damaged vasculature surface).

These arguments were considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that courts have acknowledged that patent claims are not interpreted in a vacuum, and reference back to the patent's specification for *purposes of claim interpretation* (e.g. determine what is being claimed), even in the context of double patenting, is acceptable. E.g. *In re Higgins et al.* (CCPA 1966) 369 F2d 414, 152 USPQ 103. Additionally, in satisfying the Examiner's burden of demonstrating *inherency of a claim limitation* any source of "extrinsic evidence" is permissible [(e.g. citation of

references or other evidence: See MPEP 2131.01(d); See *In re Best*, 195 USPQ 430,433 (CCPA 1977)(inherent anticipation regarding prevention);], as well as the use of "intrinsic" evidence, which include applicant's own specification . *See Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993) (Board consulted applicant's own Experimental Results to demonstrate inherency of method preamble limitation). Accordingly, for purposes or demonstrating claim limitation inherency or claim interpretation, the use of "intrinsic evidence" (e.g. within the four corners of the specification) is entirely proper; even in the context of double patenting.

Applicant's argument fails to appreciate the patent claims teaching as a whole. The '978 patent claims teach "administering" compositions comprising at least one "nitric oxide adduct" which encompass small enumerated Markush lists from which selection of compounds (e.g. low molecular weight thiols: such as nitrosothiol, nitrosated amino acid and nitrosylated hemoglobins) would be immediately "envisaged" (e.g. anticipated) or alternatively obvious to one of ordinary skill in the art as pointed out in the rejection above (see *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). With respect to anticipation and obviousness regarding a reference teaching of a limited genus or markush listing of compounds applicant is further referred to MPEP 2131.02 (anticipation) and MPEP 2144.08 (obviousness) both of which sections further discuss the *In re Schaumann* CCPA decision.

The rejection above makes reference to the '978 specification for purposes of claim interpretation and inherency. For example, the patented claim method objectives include the following:

a. treat a damaged vascular surface in which damage to the endothelium or subendothelium, narowing or stenosis of the vessel has occured (e.g. see patent claim 1);

b. wherein the method for treating ... is a method of preventing or inhibiting platelet deposition or for alleviating restenosis (e.g. see patent claim 2); and

c. wherein the nitric oxide adduct delivers at least one of a nitrosium ion or a nitroxyl ion physiological conditions (e.g. see patent claims 13 and 49);

However, while the claims broadly encompass any means of "administering" NO HOST is recited in the claims. For purposes of claim interpretation (e.g. designing around/infringement etc.) determination of the host (e.g. the recipient of the administering) is a question of claim interpretation to which "intrinsic" evidence (e.g. the '978 specification) is at issue. From the patent claims it is clear that the host to be treated must have had a disease/disorder or other malady that:

a. resulted in "a damaged vascular surface" with "narrowing or stenosis of the vessel" (corresponding to item a. above) ;

b. result in or otherwise involves aberrant platelet deposition and/or restenosis (corresponding to item b above); and/or

c. is preventable or treatable by administering an NO (e.g. nitrosium ion or a nitroxyl ion) donating compound (e.g. corresponding to item c. above).

Accordingly, although the '978 claims don't explicitly teach method diseases presently claimed (e.g. 101 double patenting is not at issue) these disease states are nevertheless implicitly taught (e.g. obvious) upon consulting the '978 specification for

purposes of claim interpretation (e.g. determining the intended disease host). Thus, the patented claim methods are directed to *in vivo* administration of compositions within the scope of those presently claimed to treat a host who possesses a disease state within the scope of the presently claimed invention since the patent method host:

b. possesess a disease/disorder resulting in the patent claims treated sequalea and/or symptoms; and/or

c. has a disorder/disease or other malady which is treatable with NO donating compounds administered by the patented methods.

Additionally, consistent with established case law (e.g. see *In re Best and Novitski*) administraion of the same composition in the same amounts to the same host would inherently result in "reducing blood pressure" (as presently claimed), especially when such an "inherent" effect is supported both by the '978 specification teaching (eg. vasodilation)and the concomitant claim teaching of the NO containing compounds ability to treat stenosis or blood vessel narrowing.

Turning to claim 40, applicant's argument regarding the patent's failure to teach "nitrosylhemoglobin" as an NO adduct is not persuasive since this argument is clearly not commensurate in scope to the presently claimed invention which encompasses "one or more nitrosyl-heme containing donors of NO" which encompasses (poly) nitrosated/nitrosylated (e.g. S-nitrosylhemoglobins) within the scope of the patented claim methods..

Accordingly, for all the reasons recited above, the double patenting rejection is hereby retained.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

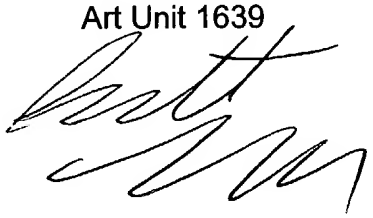
Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639



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July 2, 2004